King Saud University
College of Medicine
2nd Year, 2nd Block

GIT BLOCK

PHARMACOLOGY 433

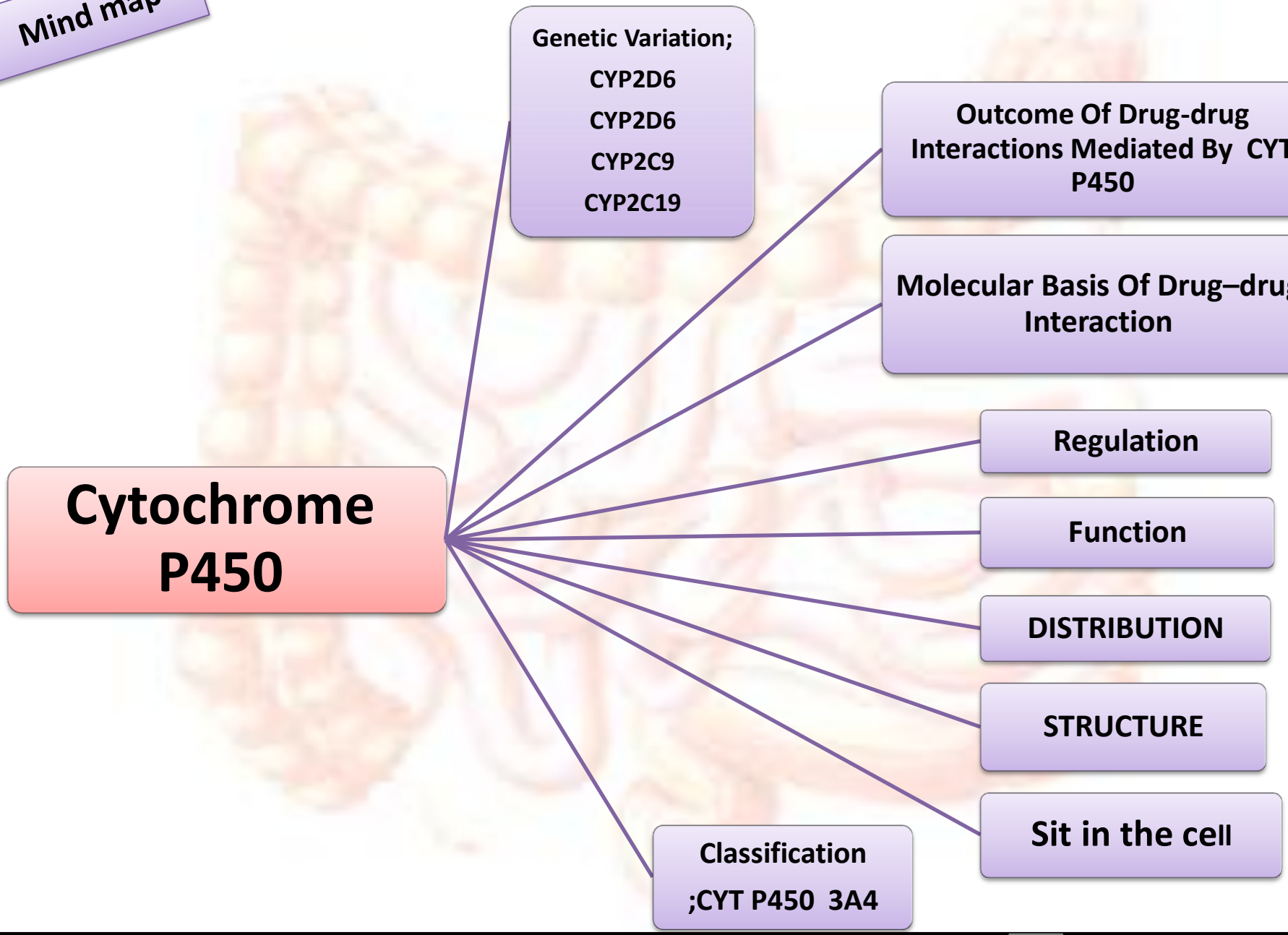
MED 433 Teams

L6: Cytochrome System and Drug Metabolism

Learning Objective

- evise the intent of drug metabolism and its different phases
- Define the role of cytochrome system in relation to drug metabolism
- Expand on the nature, location, nomenclature, structure, distribution & function of CYT P450
- Focus on its regulation; directly & indirectly, its induction & inhibition in relevance to drug interactions
- Interpret the molecular mechanism of interactions by CYT P450
- Classify its different isoforms, their substrates, inducers & inhibitors
- Delineate some of its genetic variations

Mind map



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DRUG METABOLISM

INTRODUCTION+ IMPORTANT

• Drug metabolism could happen every where in body, but MAINLY IN LIVER "METABOLIC CLEARING HOUSE".

• **Drugs identified as foreign substances that body must get rid of, Besides mostly lipophylic ➔ so the liver subjects them to chemical transformation (METABOLISM) ➔ to become inactive & easily excreted.**

→ Polar products >> Renal Elimnation.

→ Non-Polar >> Biliary Elimination.

 # Drugs have to be highly lipid-soluble to cross the cell membrane, water-soluble drugs usually have intravascular effect *Because can't cross cell membrane*.

Cytochrome System :

1. Phase I : Oxidation* / Reduction / Hydrolysis.
2. Phase II : Conjugation.

Then we will have :

• Inactive product

• Active metabolite

• A product with different effect

• Toxic metabolite

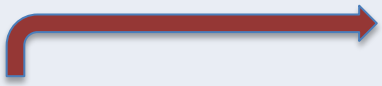
• Cyt-P450 is the terminal rate limiting oxidase of this system, shuttles electrons from molecular oxygen to oxidize the drugs. *cyt-p450 is the last stage before drug become ready to get conjugated*

Cytochrome P450 Family of Enzymes (Cyt-P450) :

It is histo not pharma= for reading

located mainly attached to the smooth endoplasmic reticulum of **hepatocytes.**

They are isolated in the subcellular fraction termed the microsomes ➔ **Liver microsomal enzymes**.



• Means *colored cells*, They color the liver cells dark red as they contain iron.

Cytochrome P450

• Absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide.

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Cytochrome P450 :

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- **Structure : They are heme-containing isoenzyme.**
- **Distribution :**
  1. **Highly concentrated in hepatocytes (LIVER).**
  2. **Enterocytes of the small intestine have the principal extra-hepatic source.**
  3. **Very small quantities in kidneys, lungs, & brain.**
- **Function : Responsible for most of the OXIDATIVE METABOLISM of:**
  1. **Endogenous substances : steroid hormones, prostaglandins, lipids.**
  2. **Exogenous compounds : diet (food & beverages) / Drugs / environmental xenobiotics.**

IMPORTANT

Regulation :

Activation or **Inactivation** of the CYT P450 can be achieved either :

1. Directly : through the enzyme itself.*drug activate cyt-p450 direct*
2. Indirectly : by expression or repression of its relevant genes by activation or inhibition of the responsible transcription factors. .*drug activate transcription factors then activate cyt-p450 *

When drugs play a role in regulation of the CYT P450 they are termed :

Enzyme Inducer : if activate the enzyme.
Enzyme inhibitor : if inactivate the enzyme.

} Drug-drug Interaction

Molecular Basis of Drug-Drug Interaction :

The nuclear receptor **PXR is a transcription factor that regulate the expression of Cyt-p450 gene**.

- If **drug A is inducer**, it bind & activate PXR which will dimerize with RXR, **the heterodimeter PXR/RXR will induce expression of Cyt-p450** which will **inhance metabolism of drug B**.
- If **drug A is inhibitor**, inactivation of PXR/RXR, repression of Cyt-p450 gene, **decrease metabolism of drug B.**

#Activation or Inactivation can be processed by any food, intrinsic products or extrinsic xenobiotics as drugs (usually the lipophylic) that have to be metabolized.

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1.CYT P450 "3A4"

(the most common, ~30%)

*3A4 related to drug metabolism not all cytochrome that much important to drug metabolism and every one has different substrates to act on

Substrates	Inhibitors= toxicity	Inducers= no response
Immunosuppressants: Cyclosporine	Immunosuppressants: Cyclosporine	
Azole Antifungals: Fluconazole	Azole Antifungals: Fluconazole	
Antibiotics: Erythromycin, Clarithromycin	Antibiotics: Erythromycin, Clarithromycin	
Ca channel blockers: Amlodepine, Verapamil	• Protease Inhibitors: Ritonavir • Cimetidine • Chloramphenicol • Nefazadone • Grape Fruits	• Rifampicin • Phenytoin • Carbamazepine • Barbiturates • Dexamethazone • Progestins
Statins: Atorvastatin		
Antiarrhythmic: Amidarone		
Cancer Chemotherapy: Cyclophosphamide, Tamoxifen		
Non-Sedating Antihistaminics: Astamizole		
Benzodiazipines: Midazolam, Clonazepam		

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2.CYP2D6

- This isoenzyme has the most frequent polymorphisms in all CYT P450.
- When polymorphism* occurs → ↓ metabolizing capacity of CYP2D6 i.e those who exhibit the polymorphism become poor metabolizers:

*It means person will develop toxicity alone !! without any increasing in dose + without any combining with other drug

1. Metabolism of some **drugs** neuroleptics, tricyclic antidepressants, antianginals agent (perihexiline), antiarrhythmics (propafenone & metoprolol) is suppressed → **so side effects & toxicity develop.**
   - Neuropathy after **therapeutic doses** of **perihexiline**.
   - Severe brady arrhythmias → heart block on **therapeutic dose** of **propafenone** or **metoprolol**.

2. The **pro-drugs** cannot be converted to their therapeutically active metabolite; e.g poor analgesia with **codeine** & **tramadole** because **they are not transformed into active forms**.

The key word for the cases , it should be **one drug + in the therapeutic doses**

Genetic Variation

Genetic polymorphisms* in CYT P450 isoenzymes have been observed & are reasons behind the altered response to drug therapy.

Warfarin+genatic variation can leads to bleeding

3.CYP2C19

- Polymorphism in CYP2C19 showes **increased & prolonged action** of its substrates as **omeprazole**.
- This has been an advantage as in those variants → ↑ cure rates in peptic ulcer patient with ***Helicobacter pylori***.

4.CYP2C9

- **Warfarin, phenytoin**, & **tolbutamide** are examples of drugs with **narrow therapeutic index that are metabolized by CYP2C9**.
- Clearance of these drugs is impaired in genetic variation of the enzyme.

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CASE:

A 50 years old, patient was treated for the last 3 years by the hypocholestrolemic agent; **atorvastatin**. Yesterday he began to complain of severe muscle pains, weakness and reddish discoloration of urine.

He receives daily **multivitamins** and his lab results last week, proved that he has become diabetic, for which he was prescribed **metformin**. He was also started on a course of **fluconazole** for a concomitant fungal infection.

From drug history, the diagnosis of his current state was likely rhabdo-myositis (severe muscloskeletal toxicity) and was verified by the lab finding of severe elevation in creatinine phosphokinase.

Which one of the following drug-drug interaction on CYT 3A4 is the likely cause of his current state?

A. Metformin + Atrovastatin

B. Atrovastatin + Fluconazole

C. Metformin + Fluconazole

D. Fluconazole + Multivitamins

Tip:

1. Underline the mentioned drugs. **(atorvastatin, multivitamins, metformin, fluconazole)**
2. Exclude the drugs that weren't mentioned in the previous list. **(multivitamins, metformin)**
3. You're left with the answer. **(atorvastatin*substrate* , fluconazole*enzyme inhibitor*)**

Answer: B

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SUMMARY

- Drug metabolism could happen mainly **in the liver.**
- **Cyt-P450 is the terminal rate limiting** oxidase of this system, shuttles electrons from molecular oxygen to oxidize the drugs.
- Cyt-P4 is Responsible for most of the **OXIDATIVE METABOLISM : endo,exo.**
- PXR is a transcription factor that regulate the expression of Cyt-P450 gene.
- Cyt-p450 gene induced: activates **PR ,** Tolerance or complete nullification , decrease efficacy.
- Cyt-p450 gene inhibited: inactivates **PXR** increase toxicity .
- Drug-drug interaction.
- the most common isoform is **CYT P450 3A4.**
- **CYP2D6: most frequent polymorphisms .**
- **Polymorphism in CYP2C19 showes increased & prolonged action of its substrates as omeprazole** variants → ↑ **cure rates** in peptic ulcer patient with Helicobacter pylori.
- **Warfarin, phenytoin, & tolbutamide are examples of drugs with narrow therapeutic index that are metabolized by CYP2C9.**

Quiz yourself

Answers 1-D 2-A 3-A 4-C 5-D 6-B 7-A 8-B 9-A

1-Where is Cyt-450 mainly present?

A. Enterocytes
B. Erythrocyte
C. Neuron
D. Hepatocytes

2-Cyt-450 is responsible for oxidative metabolism of which of the following endogenous substances?

A. Testosterone
B. Vit C
C. Grape fruit
D. Banana

3-The most common isoform is ?

A. Cyt-P4503A4
B. CYP2C19
C. CYP2C9
D. CYP3C98

4-Which of the following drugs is metabolized by CYP2C9 ?

A. Penicillin
B. Vancomycin
C. Phenytoin
D. Atrovastatin

5-Drug-Drug interaction that induces Cyt-450 will cause?

A. Toxicity
B. Immunity
C. IF
D. Tolerance

6-Drug-Drug interaction that inhibit Cyt-450 will?

A. Release CD4
B. Increase toxicity
C. Decrease toxicity
D. Increase Efficacy

7-has the most frequent polymorphisms in all CYT P450?

A. CYP2D6
B. CYP2C19
C. CYP2C9
D. CYP3C98

8-Polymorphism in which of the following increase the rate of cure in H.Pylorus peptic ulcer?

A. CYP2D6
B. CYP2C19
C. CYP2C9
D. CYP3C98

9-Do some drugs skip Phase 1 and go to phase 2 immediately ?

A. Yes
B. No
C. No enough information

Done by

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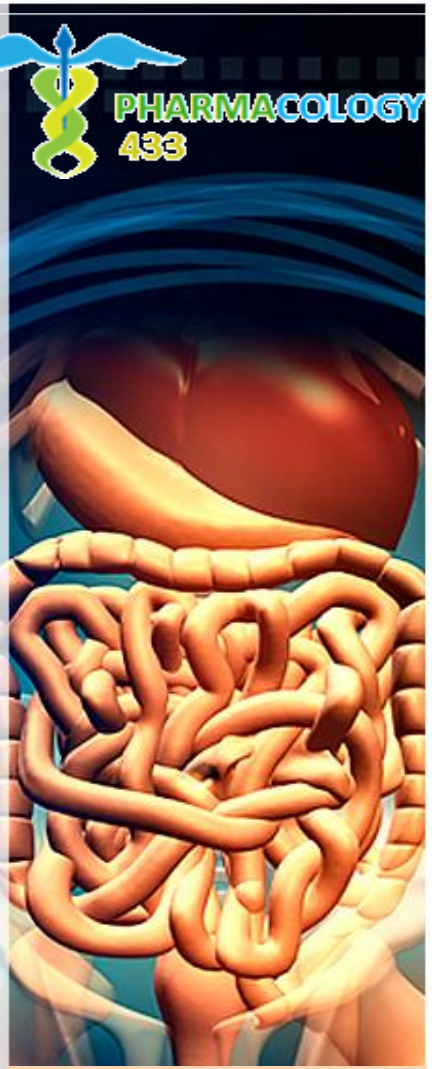
It always seems impossible until it is done

BEST OF LUCK



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